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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,377	07/10/2001	Keith D. Allen	R-365	8328

7590 05/07/2003

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/903,377	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this c mmunication appears n the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-7,11-16,20 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-30 are pending.

Election/Restrictions

Applicant's election with traverse of Group III, claims 8, 10, and 17-22 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that has not shown that a serious burden would be required to examine all the claims. This is not found persuasive because each of the Inventions requires a separate search status. In particular, it is maintained that the products of Groups I, II, III, VI, VII, VIII and X are different each from the other; they each have different chemical structures and can be used in materially different methods that require different technical considerations. For example, the DNA targeting construct of Group I can be used to disrupt a chemokine receptor 9A gene in a somatic cell *in vitro*, the cells of Group II can be used to produce a protein, the transgenic non-human animal of Group III can be used as a model of disease, the unknown agents of Group VI can be used for modulating the expression of a of chemokine receptor 9A gene in a somatic cell *in vitro*, the phenotypic data of Group VII can be used for statistical analysis in a database, the agent of Group VIII can be used for modulating a phenotype associated with a transgenic mouse, and the agent of Group X can be used as an agonist or antagonist of a chemokine receptor 9A receptor. It is maintained that the products of Inventions I, II, III, VI, VII, VIII and X are distinct due to their divergent subject matter (DNA targeting construct, cells, transgenic non-human animal, unknown agent that can modulate the expression of a chemokine

receptor 9A gene, an agent that can modulate a phenotype in a transgenic mouse, an agonist or antagonist of a chemokine receptor 9A receptor) and are separately classified and searched.

It is maintained that the methods of Groups IV, V, and IX are distinct, comprising different methodologies and using different products. For example, the method of Group V can be practiced in a somatic cell *in vitro*, while the method of Group IV is required to be practiced in a transgenic non-human animal. Moreover, the method of Group IX could comprise different classes of agents as the method embraces agents that modulate a phenotype in a transgenic mouse. It is maintained that the methods of Groups IV, V and IX are distinct as they are directed to different methods that require the use of different products that need different technical considerations and are separately searched.

It is maintained that the products of Groups I, II, III, VI, VII, VIII and X are distinct from the methods of Groups IV, V and IX; the products of Groups I, II, III, VI, VII, VIII and X can be used in methods, which require different reagents and technical considerations from the methods of Groups IV, V and IX. For example, the DNA targeting construct of Group I may be used as a probe in a hybridization assay *in vitro* while the cells of Group II may be used to produce a protein and the transgenic non-human animal of Group III may be used to produce antibodies to an antigen; the method of Group IV may be used to identify agents that modulate the expression of a chemokine receptor 9A gene; the method of Group IV may be practiced with agents that have different chemical structures from the agents of Groups VI, VII, and X. It is

maintained that the products of Groups I, II, III, VI, VII, VIII and X are distinct from and can be used in different methods (hybridization assays, generating antibodies) from the methods of Groups IV, V and IX.

Therefore it is maintained that all the inventions are distinct each from the other for the reasons given above. The requirement is still deemed proper and is therefore made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

The requirement is still deemed proper and is therefore made FINAL.

Claim 9, directed to cells obtained from a transgenic non-human animal was inadvertently omitted from the Group III claims. Claim 9 is now under current consideration.

Claims 1-7, 11-16, and 23-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Drawings

Amended figure 2A has been accepted by the Examiner. All the drawings are now accepted by the Examiner.

Claim Objections

Claim 22 is objected to because of the following informalities: the claim is directed to a cell derived from the transgenic mouse of claim 20, however claim 20 is directed to a method of making a mouse and not the mouse itself. It would appear that Applicants intended claim 22 to depend from claim 21. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10, and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic non-human animal, particularly a mouse, comprising a disruption in a chemokine receptor 9A gene, wherein the mouse exhibits a

phenotype of decreased agility, coordination, or balance. The claims are further directed to methods of making the same and cells derived from the same.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See the working example on pages 53-53-56 of the specification. The specification teaches that these knockout mice as homozygotes, exhibit a phenotype of decreased agility, coordination, or balance as compared to wild-type mice, as a result of the disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See pages 55-56 of the specification. While the specification has taught the generation of such a transgenic knockout mouse having a phenotype of decreased agility, coordination, or balance, the specification has not taught the generation of the other transgenic non-human animals comprising a disruption in a chemokine receptor 9A gene encompassed by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support the creation of other transgenic non-human animals encompassed by the claims. See pages 48-49. In addition the instant specification has asserted that the instantly claimed transgenic non-human animals may be associated with a disease and that the same or cells obtained from the same may be used for screening potential therapeutic agents. See pages 36-37. The instant specification however, has failed to correlate the observed phenotype of decreased agility, coordination, or balance of the exemplified transgenic mouse with any disease. As such the instant specification has failed to teach how to use the transgenic non-human animals embraced by the claims. In view of the lack of guidance provided

by the instant specification it would have required undue experimentation to make and use the invention as claimed.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 8, 10, and 20-21 as they read on embryonic stem cells and transgenic knockout non-human animals:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a chemokine receptor 9A gene other than a transgenic knockout mouse. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including

the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are directed to transgenic non-human animals and cells derived therefrom (claims 8-9) or methods of making a transgenic mouse by introducing a targeting construct into a cell and the transgenic mouse produced by the method and cells obtained from the same mouse (claims 10, 20, 21, 22), which all would require introduction of a transgene into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. The state of the art does not support the use of cells other than mouse embryonic stem cells for creating transgenic mice. See above. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse or use of cells other than embryonic stem cells for creating a transgenic knockout mouse.

Claim 8 encompasses transgenic non-human animals that comprise a disruption in a chemokine receptor 9A gene that do not exhibit any particular phenotype. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1

encodes a chemokine receptor 9A. In view of the unpredictability of phenotypes resulting from disruption of genes it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1. The specification discloses a phenotype exhibited by knockout mice comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1 is decreased agility, coordination, or balance. See pages 55-56 of the specification. Claim 8, as written, does not include a phenotype that differs from the wild-type mouse. Moreover the skilled artisan would know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such. The specification overcomes the unpredictability in obtaining a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1; however, claim 8 does not recite a phenotype as disclosed in the specification. Inclusion of a phenotype associated with a disruption of chemokine receptor 9A gene in a mouse in the claims would overcome this aspect of the rejection. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Claims 17-19 and 21 are directed to a transgenic mouse comprising a disruption in a chemokine receptor 9A gene having a phenotype of decreased agility, coordination or balance. The specification has asserted that the transgenic mice of the claimed invention may exhibit a disease state and that such or cells derived therefrom may be used in screening assays to identify potential therapeutic agents. See pages 36-37. The specification however, has failed to provide guidance that correlates a phenotype of

decreased agility, coordination, or balance with any disease. The specification has not provided any other uses for transgenic mice exhibiting a phenotype of decreased agility, coordination, or balance. In light of the lack of guidance provided by the specification that correlates a phenotype of decreased agility, coordination or balance with a disease, it would appear that the instant specification has failed to provide guidance that would enable the skilled artisan to use the claimed transgenic mouse. In view of the lack of guidance provided by the instant specification it would have required undue experimentation for the skilled artisan to use the claimed transgenic mouse.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a chemokine receptor 9A gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a chemokine receptor 9A gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a phenotype other than the exemplified mouse, the unpredictable state of the art with respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to all non-human animals and the lack of guidance provided by the specification for use of a transgenic mouse comprising a disruption in a chemokine receptor 9A gene having a phenotype of decreased agility, coordination, or balance, it

would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed. The claims appear to be free of the prior art but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER